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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Andres Metspalu, et al.

Serial No.: 09/741,960

Filed: December 20, 2000

For: **METHOD AND DEVICE FOR IMAGING AND ANALYSIS OF BIOPOLYMER ARRAYS**

Assistant Commissioner
for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Assistant Director for Patents, Washington, DC, 20231 on August 30, 2001.
Anne E. Pitts
Registration No. 47,861
Name of Applicant, Assignee, or Registered Representative

Anne E. Pitts
Signature
August 30, 2001

Dear Sir:

DECLARATION OF LEWIS T. CLAIBORNE UNDER 37 C.F.R. §1.132

I, the undersigned declare that:

1. I hold a B.S. degree in physics and mathematics (1957) from Baylor University, Waco, Texas.

2. I hold a Ph.D. degree in physics (1961) from Brown University, Providence, Rhode Island.

3. I have over thirty eight (38) years of industrial research experience in applications of solid-state physics with fifteen (15) years of direct experience in physical optics. I was employed at Lockheed Martin Corporation for ten (10) years and at Texas Instruments for twenty seven (27) years. In my career I have invented and developed numerous instruments and applications based on optical principles. These inventions and applications include systems for the detection of

optical/infrared signals that are directed onto patterned arrays of semiconductor material. The material in these structures responds to evanescent or fringing electrical fields from the incoming radiation. The coupling mechanism through fringing fields is very similar to that which will be produced in the fluorescent detector of the present invention. An example of an infrared detector array that I have developed is described in US Patent #6,180,990 "Hyperspectral Radiation Detector". Such detector structures have been demonstrated in a variety of compound semiconductor materials such as GaAs/GaAlAs and HgCdTe. Other Optical instruments that I have helped to develop include CCD cameras, integrated optic circuits, and thin film optical thickness measurement systems.

4. I have read the specification and claims of U.S. Patent Application 09/741,960 filed December 20, 2000, which claims priority to International Patent Application PCT/EE00/00001 filed April 20, 2000. I understand that enablement under U.S. patent law requires disclosure of the invention in the specification to be sufficient to enable a person skilled in the art to which the invention pertains to practice that which is set forth in the claims. Furthermore, I understand that the invention must be described in such full and clear terms so as to enable a person skilled in the art to practice the invention without undue experimentation.

5. I am aware that the Examiner has rejected all pending claims on the ground that the invention was not described in the specification in great enough detail to enable one skilled in the art to which it pertains, or to which it is most nearly connected, to make and use the invention. To support this conclusion, the Examiner stated that: 1) the quantity of undue experimentation in the absence of an enabling disclosure is too great; 2) the amount of guidance or direction provided in the specification is too little; 3) there are no working examples present in the specification; 4) the nature of the invention is inherently unpredictable; 5) the specification does not solve problems recognized in the state of the prior nucleic acid hybridization art; 6) the relative skill of those in the art is high, on par with those holding a Ph.D. in biochemistry; and 7) the breadth of scope of claims is too broad, encompassing a genera of devices.

6. Upon reading the specification of U.S. Patent Application 09/741,960 entitled **METHOD AND DEVICE FOR IMAGING AND ANALYSIS OF BIOPOLYMER ARRAYS**, I believe the relative skill in the art most closely associated with the claimed fluorescence detector to be on par with those educated in the field of physics, and specifically in the field of physical optics.

7. I find, as a person skilled in the relative art, that the specification of U.S. Patent Application 09/741,960 is enabling, in that it explains how to make and use the claimed fluorescence detector. The components of the claimed fluorescence detector are readily commercially available and the specification demonstrates how the components are arranged and function. I believe that the amount of experimentation necessary for a person skilled in the art to make and use the claimed invention is minimal. I believe that the amount of direction or guidance provided in the specification is adequate for a person skilled in the art to make and use the claimed fluorescence detector. I find that the specification and drawings exemplify a working example of the claimed fluorescence detector. Because the claimed fluorescence detector is based on accepted physical and optical principles, I believe that the nature of the invention, although complex, is not unpredictable.

8. From observing Fig. 3-5 in addition to reading the specification particularly at pages 4-6, I understand how each component of the invention relates to one another. I understand that the light source (2) has the ability to excite at least one fluorophore. The light source (2) is directed to the waveguide support (1) to cause total internal reflection by multiple components: a transparent hexahedron (4), an optical wedge (5), a mirror (6), and/or a prism (8). The transparent hexahedron (4) is rotated around the axis perpendicular to the light beam to more efficiently direct the light beam into the waveguide support (1) at an angle under which total internal reflection is generated. The optical wedge (5) is rotated around the axis approximating the light beam also to more efficiently direct the light beam into the waveguide support (1) at an angle under which total internal reflection is generated. The mirror (6) and/or prism (8) can also be used to reflect

and guide the light beam into the waveguide support (1). In order to minimize the transitional loss of light from the prism (8) to the waveguide support (1), a transparent liquid (9) can be used if its refractive index is approximately equal to the refractive indices of the prism (8) and waveguide support (1). The cylindrical lens (3) functions to intensify the resulting total internal reflection by focusing the fan into a fan shape thinner than the edge of the waveguide support (1). Emission spectra are detected by a digitally controlled cooled charge – coupled – device camera (CCD) (7) and the data generated stored in a digital system, such as a personal computer.

9. As a person skilled in the art of physical optics, I believe that this invention represents a practical embodiment of an instrument for achieving the intended operational function. The claimed fluorescence detector is a viable instrument to provide a high signal to noise image of fluorescent excitation and emission. I understand that this characteristic of the claimed fluorescence detector makes it especially useful for analyzing thousands of fluorescently – labeled nucleic acids attached to a chip, which is currently the state of the art.

10. I declare that I am an independent consultant with no relationship, personal or monetary, with any applicant or inventor U.S. Patent Application 09/741,960 entitled **METHOD AND DEVICE FOR IMAGING AND ANALYSIS OF BIOPOLYMER ARRAYS.**

11. I further declare that all statements made herein of my own personal knowledge are true and that all statements made on information and belief are believed to be true. Furthermore, these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment or both under §1001 of Title 18 of the United States code, and that such willful false statements jeopardize the validity of the above-mentioned application or any patent issuing thereon.

Lewis T. Claiborne	Lewis T. Claiborne	August 15, 2001
Name of Person Signing	Signature	Date

Curriculum vitae
of Ants Kurg

Date and place of birth: December 19, 1962, Viljandi, Estonia
Citizenship: Estonian
Personal status: Married, two daughters
Address home: 3 Liivakuru St., Tartu, ESTONIA
Address work: Institute of Molecular- and Cell Biology, Tartu University, 23 Riia St., 51010 Tartu, ESTONIA
Tel: (+372) 7 375 029; Fax: (+372) 7 420 286; e-mail: akurg@ebc.ee

Education:
1986 - Tartu State University, Estonia; Faculty of Biology and Geography, *cum laude* as biochemist
1988 - Three months visiting scientist at Shemjakin Institute of Bioorganic Chemistry, Moscow, Soviet Union, Dr. Elena Frolova laboratory.
1989 - From May to June visiting scientist at Humboldt University of Berlin; GDR Faculty of Veterinary Medicine, Institute of Biochemistry, Prof. Siegfried Risse laboratory.
1991 - From September to December, visiting scientist at Humboldt University of Berlin; Germany. Faculty of Veterinary Medicine, Institute of Biochemistry, Prof. Siegfried Risse laboratory.
1992 - From July to August and from November to December, visiting scientist at Humboldt University of Berlin, Germany. Faculty of Veterinary Medicine, Institute of Biochemistry, Prof. Siegfried Risse laboratory.
1993 - From September to December, research grant from EEC to study retroviral vectors based on BLV, at Free University of Berlin, Faculty of Veterinary Medicine, Institute of Virology Prof. Dieter Ebner laboratory and Institute of Biochemistry, Prof. Siegfried Risse laboratory
1996 - Ph.D., in Molecular Biology
Title of Ph.D. thesis: Bovine Leukaemia Virus: Molecular Studies on the Packaging Region and DNA Diagnostics in Cattle
Advisor: Prof. Andres Metspalu, MD, Ph.D.

Languages: Estonian (native language), Russian, German and English

Professional employment:
1986 - 1991 Junior research scientist at the Laboratory of Gene Expression; Institute of General- and Molecular Pathology; Tartu State University
1991 - 1997 Research scientist at the Chair of Biotechnology; Institute of Molecular- and Cell Biology; University of Tartu
May 1997- Summer 1998 Postdoc at the Dept of Molecular and Human Genetics; Baylor College of Medicine; Houston; Texas; USA.
1998-1999 Senior research scientist at the Chair of Biotechnology; Institute of Molecular- and Cell Biology; University of Tartu
1999-present Docent of Biotechnology at Chair of Biotechnology; Institute of Molecular- and Cell Biology; University of Tartu

Since 1987 I have studied the molecular biology and diagnostics of bovine leukemia virus (BLV). We have defined the sequences necessary for the encapsidation of genomic RNA of this virus and constructed several proviral vectors based on this virus. We have studied different PCR-based methods for diagnosis of BLV infection and worked out our own high-sensitivity methods. This research was summarised in my Ph.D. thesis in 1996.
At present, my research interests are: Developing and applying of new DNA diagnostic methods based on APEX technology

Teaching:
Since 1991, I have supervised diploma works at Chair of Biotechnology.
1993 - present. I have lectured in, and I am currently in charge of the general and molecular biotechnology.

1. Sommer,G., Kurg, A., Wagner, H.-J., Heymann, S., Blankenstein, P. and Ebner, D.: Untersuchungen zur Lage eines vermuteten Verpackungsortes im Genom des Bovinen Leukosevirus. *Mh.Vet.-Med.* 1990, **45**: 713-716.
2. Heymann, S., Sommer, G., Frolova, E. J., Dolganov, G.M., Kurg, A., Wagner,H.-J., Blankenstein, P., Risse, S.; Rinder-Retrovirusvektoren, Verfahren zu ihrer Herstellung. Patent: WP C 12N/340 144.3 1990
3. 3. Sommer, G., Wagner, H.-J., Bondzio, A., Blankenstein, P., Heymann, S., Kurg, A.: Construction of retroviral vectors based on BLV sequences to manipulate eukaryotic cells. *Biological Chemistry Hoppe-Seyler* 1991, vol. 372, **8,** 756.B
4. Bondzio, A., Blankenstein, P., Kurg, A., and Kinder, E. 1994. Enhancement and Inhibition of BLV Expression in Different Infected Cell Lines. *Biological Chemistry Hoppe-Seyler* vol. 375, Sept. p.35.
5. Kurg, A., Sommer, G., Metspalu, A. An RNA Stem-Loop Structure Involved in the Packaging of Bovine Leukemia Virus Genomic RNA *in vivo*. *Virology* 1995, **211**, 434-442.
5. Fechner, H., Kurg, A., Blankenstein, P., Mewes, G., Geue, L., Albrecht, C. and Ebner, D. (1996) Direct use of cell lysates in PCR-based diagnosis of bovine leukemia virus infection. *Berl. Münch. Tierärztl. Wschr.* **109,** 446-450.
6. Fechner, H., Kurg, A., Geue, L., Blankenstein, P., Mewes, G., Ebner, D. and Bsier, D. (1996) Evaluation of Polymerase Chain Reaction (PCR) Application in Diagnosis of Bovine Leukaemia Virus (BLV) Infection in Naturally Infected Cattle. *Journal of Veterinary Medicine* **B 43**, 621-630.
6. Fechner, H., Blankenstein, P., Looman, A. C., Elwert, J., Geue, L., Albrecht, C., Kurg, A., Beier, D., Marquart, O. and Ebner, D. Provirus Mutants of the Bovine Leukemia Virus and their Relation to the Serological Status in Naturally Infected Cattle. (1997) *Virology* **237**, 261-269
7. Pastinen, T., Kurg, A., Metspalu, A., Peltonen, L. and Syvänen, A.-C. Minisequencing: A specific tool for DNA analysis and diagnostics on oligonucleotide arrays. (1997) *Genome Research* 7 ,606-614.
8. Metspalu, A., Saulep, H., Kurg, A., Tõnisson, N., Shumaker, J.M. Primer extension from two-dimensional oligonucleotides grid for DNA sequencing analysis. In: Genomics: Commercial opportunities from a scientific revolution. Ed. By G.K. Dixon, L.G. Copping, D. Livingstone. BIOS Scientific Publishers (1998) ISBN 1-85996-106-1, pp.217-219.

9. Kurg A, Tõnisson N, Metspalu A, Berik E. Laser diagnostic system for rapid mutation identification. (1999) *Medical and Biological Engineering and Computing* 37, suppl. 1, 311.
10. Andres Metspalu, Krista Kaasik, Neeme Tõnisson and Ants Kurg. Oligonucleotide array for mutation analysis in familial breast cancer. (1999) Disease Markers **15** (1-3), 117.
11. Tõnisson, N., Kurg, A., Lõhmussaar, E., Metspalu, A. Arrayed primer extension on the DNA chip: method and applications. In: "Microarray Biochip Technology" Ed by Mark Schena (2000) BioTechniques Books, Eaton Publishing. ISBN 1-881299-37-6, 247-263.
12. Tõnisson N, Kurg A, Kaasik K, Lõhmussaar E, Metspalu A. Unravelling Genetic Data by Arrayed Primer Extension. *Clinical Chemistry and Laboratory Medicine* 2000, **38 (2)**, 165-177.
13. Kurg, A., Tõnisson, N., Georgiou, I., Shumaker, J., Tollett, J., Metspalu, A. Arrayed Primer Extension: Solid phase four-color DNA resequencing and mutation detection technology (2000) *Genetic Testing* **4(1)**, 1-7.

CURRICULUM VITAE
ANDRES METSPALU

Date and place of birth: March 11, 1951, Estonia

Marital status: Married, four children

Citizenship: Estonian

Home:
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Education:

M.D.
Tartu University
Date of graduation: June 1976

Ph.D., in Molecular Biology
Field of study: Structure and function of the eukaryotic ribosome
Institute of Molecular Genetics, Ukrainian Acad. of Sciences, Kiev
Advisor: Prof. Artur Lind, M.D. and D.Sc.
Date of graduation: December 1979

Postdoctoral Research:

1. Columbia University, New York, USA. Prof. Alex Tzagaloff laboratory (1981-1982)
2. Yale University, New Haven, USA. Prof. Joan Steitz laboratory (1982)
3. European Molecular Biology Laboratory (EMBL), Heidelberg, Germany. Prof. Riccardo Cortese laboratory. Two month fellowship from European Society of Biochemistry (FEBS) 1985
4. Max-Planck Institute of Molecular Genetics, Wittman, West-Berlin, Germany. One month fellowship from European Molecular Biology Organization (EMBO) 1988
5. FEBS Advanced Course, May 1991, Patras, Greece. "Application of DNA Methods for the Diagnosis of Human Disease". FEBS fellowship.
6. Visiting scientist at University of Tampere, Finland. From October to November 1991
7. Visiting scientist at Hamburg University, Dept. of Molecular Biology, Germany. Prof. Joachim Kruppa laboratory. Two months fellowship from DAAD (1991-1992)
8. Research grant three months in 1993 from EEC to study hRP protein S6 gene at University of Hamburg, H. Pette Institute for Experimental Immunology.

Professional History:

1976-1980 Junior scientist at the Laboratory of Molecular Biology, Tartu University. I studied RNA-protein interactions in rat liver ribosomes and developed an affinity chromatography approach to monitor protein bindings to immobilized RNA. This research was summarized in my Ph.D. thesis in 1979.

1982-1984 Senior scientist at the Laboratory of Molecular Biology, Tartu University. During that period I was responsible to introduce recombinant DNA methods into our laboratory.

1985-1986 Head of Laboratory of Gene Expression, Tartu University.

1986-1992 Research Director of the Estonian Biocentre. I directed a research group focused on isolation and characterization of human ribosomal protein genes. We could isolate several new cDNA clones and have characterized them. I was also responsible and worked actively in developing a subunit vaccine against *E.coli* K99 infection in young calves and studied bovine leukemia virus (BLV) trying to use it as a DNA transfer vector. This study was completed in 1996.

July 1992 - present
Full professor of Biotechnology at University of Tartu.

1993-1994 Sabbatical leave, visiting professor at Baylor College of Medicine, Dept. of Molecular and Human Genetics with Prof. C.T. Caskey.

February 1996 -Second appointment as Head of Molecular Diagnostics Centre at Tartu University Children's Hospital.

1999-2000 IARC, Lyon France, the visiting scientist award

From 1991 I am developing and applying different DNA based methods for diagnosing human genetic diseases (CF, DMD, FraX, LDLR, PKU, MCAD, BRCA1, BRCA2 etc.). Main interest is to develop highly parallel and roboust arrayed primer extension technology for DNA microchips.

At present, my research interests are:

1. Fundamental questions of human gene structure, function and organization. Special interests are human disease genes.
2. Developing new oligonucleotide array - based mutation analysis methods and applying DNA diagnostics for detecting human genetic diseases, genotyping, gene expression and resequencing.

EC grants:

1995-1997 EU PECO grant #ERBCIPDCT940260 "Protein Phosphatase in Malignant Transformation and the Regulation of the Cell Cycle: their Role as Tumour Suppressors"

1995-1996 EU PECO grant #ERBCIPDCT940220 "Coordination of Cystic Fibrosis Research and Therapy"

1995-1997 EU COPERNICUS grant #ERBCIPACT940148 "Development of a new molecular diagnostic method based on primer extension with fluorescent ddNTP from immobilized disease specific oligonucleotides"

1998-2000 EC INCO-COPERNICUS #IC15-CT98-0305 "Multicenter project on genotype-phenotype-correlation in MEN I and HNPCC"

1998-2000 EC INCO-COPERNICUS #IC15-CT98-0309 "Universal DNA-chip for diagnosis of genetically inherited diseases"

Teaching:

1980-present. I have supervised diploma works, M.Sc., M.D. and Ph.D. students at Department of Molecular and Cell Biology, Faculty of Medicine and Estonian Biocentre.

1989-present. I have lectured in, and I am currently in charge of the undergraduate courses in molecular biotechnology, molecular diagnostics and gene therapy, and advanced molecular biotechnology for graduate students at Tartu University.

Miscellaneous:

1980 - Soviet Estonian Prize for Sciences

1988-1990 - Member of the Expert Council of Soviet Union Human Genome program

1988-present - Member of the Scientific Committee for Ph.D. thesis at IMCB of University of Tartu

1991-present - Member of European Society of Human Genetics

1995-present - Member of HUGO

1996-present - Member of Tartu University Council

1996-present - Member of the Committee for Estonian Prize for Science

1997-2000 - Member of Estonian Council of Scientific Competence (advisory body for distributing and supervising funds for science)

1999-present - Member of Estonian Genome Centre Foundation Council

1999-present - Estonian Society of Human Genetics: The Board member

2000 -present - European Society of Human Genetics: The Board member

2000-present - Estonian Human Gene Heredity Project: The Board member

2001 - Order of the Estonian Red Cross

Andres Metspalu

CURRICULUM VITAE

Family Name: **BERIK**
First Name: **Evgeny**
Date of Birth: 02/04/54
Nationality: Estonian

Education:

1977	Dip. physicist (lasers and laser spectroscopy) Moscow Physical Technical Institute
1986	Ph.D. in Quantum Electronics, Institute of General Physics, Moscow

Present position: President, ESTLA Ltd

Key Qualifications:

Since 1988 Dr. Evgeny Berik is the president of private R&D company ESTLA Ltd. Company works in the field of design and manufacturing of tunable lasers and laser based custom systems for scientific and applied aims (fluorescent diagnostics, medicine, telecommunications and show business). Optical workshop, fine mechanics design and manufacturing, electronics & programming service.

Career History:

1988 to the present time	President of R&D company ESTLA Ltd.
1986 - 1990	Senior Research Scientist, Institute of Physics Estonian Ac. Sci. Consult of Ministers of USSR price for the development of the systems for laser diagnostics.
1982 - 1986	Research Scientist, Institute of Physics Estonian Ac. Sci.
1980 - 1982	Junior Research Scientist, Institute of Physics Estonian Ac. Sci. Head of the group/laboratory of tunable lasers Study of the radiation characteristics of laser pumped dye lasers, non-linear transformation of tunable laser radiation, laser spectroscopy with tunable lasers. Design of special dye-laser systems for variety of applications (plasma diagnostics, environmental monitoring, space research, investigation of new laser materials) USSR price for young scientists for developments in the field of dye lasers.
1976 - 1980	Junior Research Scientist, Institute of Spectroscopy, USSR Ac. Sci., Moscow (laboratory of spectroscopic laser research) Intracavity absorption spectroscopy of with CW dye lasers
1971 - 1977	Student of 1...IV courses of faculty of General and Applied Physics, Moscow Physical-Technical Institute

Publications:

Total list of the publications includes 36 publications and 7 patents of USSR

E.Berik, *Statistical properties of Pulsed Dye Laser Radiation,* Preprint F-35, Institute of Physics Estonian Ac. Sci., 1986

E.Berik et. all, *Laser Radiation Frequency SRS Converter in Compressed Hydrogen with Low Excitation Threshold,* Sov. Quant. Electronics, 13 No.8, 1986

E.Berik et. all, *Stimulated Raman Scattering of Dye Laser Radiation in Hydrogen, Improvement of Spectral Purity,* Opt. Commun, 1987

E.Berik, *Thermal Effects in the Excimer Pumped Dye Lasers*, invited paper, Proceedings of the International Conf. Lasers 88, Lake Taho, USA

E.Berik, *Tunable lasers*,. USSR patents 910100, 1114288, 1391422